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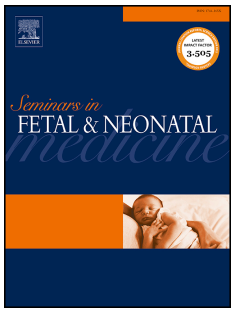

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The prediction of preterm delivery: what is new?

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SUMMARY

Preterm birth, defined as birth occurring prior to 37 weeks gestation, is a serious obstetric problem accounting for 11% of pregnancies worldwide. It is associated with significant neonatal morbidity and mortality. Predictive tests for preterm birth are incredibly important, given the huge personal, economic, and health impacts of preterm birth. They can provide reassurance for women who are unlikely to deliver early, but they are also important for highlighting those women at higher risk of premature delivery so that we can offer prophylactic interventions and help guide antenatal management decisions. Unfortunately, there is unlikely to be a single test for predicting preterm birth, but a combination of tests is likely to improve clinical prediction. This review explores the clinical utility of the currently marketed predictive tests for preterm birth in both singleton and multiple pregnancies, as well as discussing novel predictive tests that may be useful in the future.

Keywords:

Premature birth

Prediction tests

Biomarkers

Cervical length

Multiple pregnancies

1. Introduction

Preterm birth, delivery before 37 weeks gestation, is a major obstetric and global health problem. It is the largest direct cause of mortality in infants aged <5 years and associated with serious morbidity in the surviving infants [1,2]. Worldwide, 15 million babies are born prematurely, representing a preterm birth rate of 11.1% [3]. Advances in neonatology over the last few decades have resulted in increased survival rates, particularly among extremely premature infants, but this also has been associated with a subsequent increase in morbidity. This is represented in the 2015 Global Burden of Disease study, where preterm

birth is ranked fifth in the leading causes of disease burden over time [4]. Preterm birth can be either spontaneous or iatrogenic, with ~75% occurring spontaneously [5]. The pathogenesis of spontaneous preterm birth remains poorly understood and accumulating evidence suggests that it is a complex syndrome in which there are multiple attributable causes [6].

Predictive tests for preterm birth are incredibly important, given the huge personal, economic, and health impacts of preterm birth. These tests may provide reassurance for women who are unlikely to deliver early, but they are also important for highlighting those women at higher risk of premature delivery so that we can offer interventions in high-risk asymptomatic women, such as progesterone or cervical cerclage, or immediate treatments in symptomatic women including tocolysis, antenatal corticosteroids, in-utero transfer to tertiary centres, and magnesium sulphate for neuroprotection.

Several predictive tests are currently being marketed for preterm birth. The clinical utility of these tests in prediction is often very confusing as studies are often conflicting and dependent on the population studied. This review explores both the current predictive tests used in clinical practice, as well as novel emerging tests, and discusses the clinical utility of these tests in relation to the different groups of women at risk of preterm delivery.

2. Singleton pregnancies: asymptomatic high-risk women

The strongest predictor of preterm birth is a previous preterm birth or late miscarriage; these are associated with a 32% chance of a recurrent preterm birth [7]. Women with a previous preterm birth or late miscarriage, as well as those who have had previous cervical excisional surgery, are generally included in this group of asymptomatic women deemed to be at high risk of preterm birth.

2.1. Ultrasound

2.1.1. Cervical length measurement

Transvaginal sonographic assessment of the cervix has long been used as an effective tool for predicting preterm birth. A recent systematic review of clinical guidelines for preterm birth prevention has shown a consensus globally for cervical length screening among high-risk women [8]. A mid-trimester cervical length of 25 mm is generally considered to be short as it corresponds to the 10^{th} percentile in this gestational age group [9]. However, it is also clear that there is a continuum of risk related to cervical length, and research analysis around fixed thresholds should not limit its clinical utility. The shorter the cervix, the higher the risk, and this risk is not linear. Even a long cervix, >40 mm, in the mid-trimester is associated with higher rates of labour dystocia and subsequent caesarean section in labour at term [10]. A short mid-trimester cervix is one of the strongest risk factors for a spontaneous preterm birth [9,11]. A prospective blinded observational study showed that the finding of a short mid-

trimester cervix in women, with a history of previous preterm birth, conferred a relative risk for spontaneous preterm birth of 3.3 [9]. In addition, serial cervical length screening up until 24 weeks gestation significantly improved prediction of preterm birth compared with an isolated cervical length measurement.

The cervical length physiologically shortens with increasing gestation and so the earlier the gestation that a short cervical length is determined, the increased likelihood of a subsequent preterm birth [12]. Unfortunately, meta-analyses of cervical length screening are limited by the variety of gestational ages at which screening was performed, the different cervical length cut-offs (ranging from 15 to 30 mm) and the defined gestational age groups of preterm birth evaluated [13]. Furthermore, cervical length screening is dependent on a trained operator, with evidence that >25% of images may not meet standard requirements [14]. There is also conflicting evidence over the most beneficial time for cervical length measurements [15], although serial cervical length screening, as discussed above, and rate of change appear to add additional predictive value [16].

Universal cervical length screening has been implemented by some individual practitioners, although the debate remains over its clinical utility and cost-effectiveness in the low risk population [17–20] and this is reflected in the recent systematic review of preterm birth clinical guidelines where the international consensus deemed universal screening ineffective [8].

The addition of cervical length measurement to biochemical testing appears to enhance predictive accuracy and is likely to represent the best method for preterm birth prediction in this group of women in the future [21].

2.1.2. Additional ultrasound parameters

The sonographic presence of dense hyperechogenic matter in the amniotic fluid close to the internal os is known as amniotic fluid sludge. Amniotic fluid sludge has been found to be an independent predictor of preterm birth in asymptomatic women [22,23], and the combination of a short cervix and sludge confers improved prediction for preterm delivery at <28 weeks gestation (OR: 14.8; compared with OR: 9.9 for sludge alone) [24].

In recent years, there has been interest in developing new techniques to assess changes in the cervix that could help to improve prediction of preterm delivery in asymptomatic high-risk women. The cervical consistency index, determined using antero-posterior diameter measurements of the cervix with and without cervical pressure, has been shown to be a predictor at least comparable to cervical length for preterm birth, although external validation and larger sample sizes need to be considered to further assess clinical utility [25].

2.2. Biomarkers

2.2.1. Fetal fibronectin

Fetal fibronectin (fFN) is an extracellular matrix glycoprotein found between the chorion and decidua. It is normally detectable in the cervico-vaginal fluid in pregnancy before the fusion of the decidua and fetal membranes and becomes undetectable from 18 weeks gestation. Thereafter, release into the cervico-vaginal fluid is by presumed inflammatory or mechanical disruption to the chorio-decidual interface and is associated with an increased risk of preterm birth.

Fetal fibronectin is increasingly used in Europe and North America as a prediction test in asymptomatic high-risk women, as well as in women presenting with symptoms of threatened preterm labour. It was initially used as a qualitative test, in which results of 50 ng/mL are classified as positive, with its main benefit being its high negative predictive value [26], although this is related to low prevalence and sensitivity is <90%.

Quantitative fFN, the measure of absolute concentration of fFN, has been demonstrated to improve prediction compared with the qualitative test in this cohort of asymptomatic women. The EQUIPP study (Evaluation of a Quantitative Instrument for the Prediction of Preterm Birth) was the first prospective study to show the enhanced value of quantitative testing. For asymptomatic high-risk women, the use of multiple fetal fibronectin thresholds (10, 50, 200 and 500 ng/mL) increased the positive predictive value for preterm birth [27]. fFN testing alongside cervical length measurements has been shown to improve predictive accuracy and risk stratification among high-risk asymptomatic women. In the EQUIPP cohort, a combination of fetal fibronectin and cervical length was superior to fFN testing alone and quantitative fFN helped to discriminate risk in women with a short cervical length [21,27].

2.2.2. Inflammatory markers and cytokines

Preterm birth is strongly associated with inflammation and infection, and so considerable attention has been placed on determining alternative biomarkers that could identify the early inflammatory process occurring in asymptomatic women [28]. Interleukin (IL)-6, which is commonly linked to the prematurity-associated fetal inflammatory response syndrome, has been found to be increased in mid-trimester cervical secretions of asymptomatic women who deliver preterm birth [29]. In support of this, recent data has shown that the pro-inflammatory cytokines IL-1B and RANTES (Regulated on Activation, Normal T Expressed and Secreted), in mid-trimester cervico-vaginal fluid, correlate with quantitative fetal fibronectin levels and remain raised in women who subsequently deliver prematurely [30]. Although promising, these tests would need validation in larger studies and the development of point-of-care rapid assay kits for them to be useful clinically.

2.2.3. The -omes

The association between the vaginal microbiome and the risk of preterm delivery has gained huge interest in recent years and may help to predict delivery in high-risk asymptomatic women [31]. However, due to the high cost and labour-intensive nature of bacterial 16S DNA sequencing techniques, translating these associations into a clinically relevant predictive test is still in the development stage. Other promising tests include the detection of specific vaginal metabolome and micro-RNA signatures as predictors of preterm birth [32,33].

3. Singleton pregnancies: symptomatic women in threatened preterm labour

It is unlikely that one predictive test will predict all cases of spontaneous preterm delivery. The optimal tests to predict delivery in women presenting in threatened preterm labour are likely to be different from those described above for asymptomatic high-risk women. The benefits of predicting delivery within seven days in this group allow for appropriate hospital admission, in-utero transfer and antenatal management including tocolysis, antenatal corticosteroids, and magnesium sulphate.

3.1. Ultrasound

3.1.1. Cervical length measurement

In the UK, the National Institute for Health and Care Excellence guidelines on Preterm Birth management advises that cervical length measurements are performed in women presenting with symptoms of threatened preterm labour beyond 30 weeks gestation. Their recommendations, based on reviewing 15 studies, advise that if the cervical length is below 15 mm, admission and antenatal treatment should be commenced as above. This is based on moderately useful positive and negative predictive values of delivery within 48 h with a cervical length of <15 mm [34]. This also illustrates how different thresholds are used for different indications.

A recent systematic review and meta-analysis of RCTs using individual patient-level data concluded that knowledge of the cervical length in symptomatic women was associated with a significant reduction in preterm birth before 37 weeks (RR: 0.64; 95% CI: 0.44–0.94) [35]. However, the other outcomes, including delivery before 28 weeks gestation and time from testing to delivery, were not different. The biological plausibility of these findings is unknown, but knowledge of delivery risk is primarily used to inform management options unrelated to preventing preterm birth but to improve neonatal outcomes. Cervical length therefore remains valuable. Indeed, prolonging pregnancy in threatened preterm labour may be harmful if there is subclinical infection, freequently associated with preterm labour at earlier gestations.

3.2. Biomarkers

3.2.1. Fetal fibronectin

The qualitative fFN test has traditionally been used as a test for detecting imminent delivery in women with threatened preterm labour. The greatest value of this qualitative test lies in its high negative predictive values, and so it can be a useful test in reassuring women with a negative result [36].

Quantitative fFN has largely superseded the qualitative test as a predictor of imminent delivery, allowing clinicians to use different thresholds to define risk. A prospective cohort study of 300 women in threatened preterm labour showed that fFN concentration correlated with risk of preterm delivery [37]. For fFN levels <10 ng/mL, there was a negative predictive value of 98.2% for delivery before 34 weeks, whereas levels >200 ng/mL were associated with a positive predictive value of 37% for delivery before 34 weeks. The additional risk stratification of quantitative fFN may help to guide clinicians on identifying women requiring intervention and admission. The QUiPP app, a clinical prediction tool for spontaneous preterm birth, which defines a percentage risk of preterm birth based on gestation, obstetric history and quantitative fetal fibronectin, has been shown to accurately guide management at certain risk thresholds to avoid unnecessary intervention in low-risk women [38]. The advantage of the app is that it combines clinical history and interrogates risk across the whole range of fibronectin and cervical length.

The addition of cervical length measurements to quantitative fFN levels has been investigated in several studies and is likely to add value for the prediction of preterm delivery [36,39,40]. In addition, a recent economic evaluation has shown cost savings when cervical lengths between 15 and 30 mm are combined with fFN in symptomatic women [41].

3.2.2. Phosphorylated insulin-like growth factor binding protein-1 (PIGFBP-1)

PIGFBP-1 is synthesised in placental decidual cells and is thought to be released into the cervico-vaginal fluid when contractions occur as a result of damage at the chorio-decidual junction [42]. A systematic review studying data from 43 studies showed that the test has predictive ability for preterm birth, with a pooled sensitivity and specificity of 67% and 77% for delivery within seven days of testing, but it may have some role in identifying women at low risk of delivering within 48 h [43]. Recent prospective observational studies have shown high negative predictive values, but poor positive predictive values, supporting its use as a helpful “rule-out test” [44]. There are plans to develop a quantitative version of this test, potentially improving its clinical utility.

A large prospective cohort study has shown no improvement in the predictive accuracy of PIGFBP-1 when used in combination with cervical length [45]. However, post-

hoc analysis of frozen samples from a large cohort in the Netherlands showed that this test, in combination with cervical length, is comparable to fetal fibronectin and cervical length for the prediction of preterm delivery within seven days [39].

3.2.3. Placental alpha-macroglobulin-1

Placental alpha-macroglobulin-1 (PAMG-1) is a glycoprotein synthesised in the decidua and found in high concentrations in the amniotic fluid. This test was originally developed as a predictive test for rupture of the membranes; however, recent data have shown that it may be useful in predicting labour in symptomatic women with intact membranes [46]. The data are conflicting regarding PAMG-1's predictive accuracy but it has efficacy comparable at least to qualitative fetal fibronectin [46,47]. One study has shown PAMG-1 to have a higher positive predictive value than fFN for predicting preterm labour [46]. These studies also highlight the rarity of preterm birth in women presenting with symptoms of threatened preterm labour, emphasising the need for much larger studies [46,48].

3.2.4. Cervical acetate levels

Cervico-vaginal acetate levels have recently been shown to be useful in predicting preterm delivery in symptomatic women [49]. Acetate is produced in large amounts in female vaginal microbiota dominated by mixed anaerobes. An association between lactobacillus depletion and vaginal dysbiosis leading to poor pregnancy outcomes, such as preterm birth and late miscarriage, has long been reported [50]. Although the use of this metabolic marker is still in the development stages, it has been validated in a commercially available enzyme-based spectrophotometric assay kit and so may be have a future role as a clinically relevant biomarker, in combination with cervical length and fFN [49].

4. Multiple pregnancies

This risk of prematurity associated with multiple pregnancy is significantly higher than that in singletons and occurs in >50% of such cases. Although iatrogenic preterm delivery is increased in higher-order pregnancies due to an increased prevalence of complications such as pre-eclampsia, fetal growth restriction and multiple-pregnancy-specific conditions such as twin–twin transfusion syndrome, spontaneous preterm birth is also more prevalent. It has been purported that the mechanisms responsible for this are disparate from those associated with preterm birth in singleton pregnancies and may include the effects of additional uterine distension [28], increased secretion of mediators such as corticotrophin-releasing hormone from the larger placental mass, and increased levels of factors produced by the maturing fetal lung such as surfactant protein A, which stimulates myometrial contractility [51]. Currently the standard treatment modalities used in singleton pregnancies have been considered to be less efficacious in multiple pregnancy, but recent literature has indicated that

screening may accurately predict women at high risk of preterm birth. This is of particular relevance given the increased neonatal planning required for twins and higher-order multiple births.

As mentioned above, a previous preterm delivery is the most significant risk factor for preterm birth in singleton pregnancies, and women with a current multiple pregnancy and a previous history of PTB are more likely to deliver preterm [52]. However, there is currently paucity in the literature regarding the association between additional risk factors, such as previous cervical procedures and uterine abnormalities, and spontaneous preterm birth in multiple pregnancies.

5. Multiple pregnancies: asymptomatic women

5.1. Ultrasound

5.1.1. Cervical length measurement

Two meta-analyses have identified an association between a short cervix in asymptomatic women with multiple pregnancies and an increased risk of preterm birth. Conde-Agudelo et al. evaluated 16 studies assessing the measurement of cervical length using transvaginal ultrasound at 20–24 weeks gestation for the prediction of preterm birth in twin pregnancies [53]. A cervical length <20 mm predicted preterm birth at <32 and <34 weeks (pooled sensitivities, specificities and positive and negative likelihood ratios of 39% and 29%, 96% and 97%, 10.1 and 9.0 and 0.64 and 0.74 respectively) and <25 mm predicted preterm birth at <28 weeks (pooled positive likelihood ratio of 9.6). However, this meta-analysis also revealed that a cervical length >25 mm had less value as a negative predictive tool as the likelihood ratios generated only minimal changes in the pre-test probabilities of preterm birth [54]. Lim et al. evaluated 21 studies: gestational age at screening ranged from 15 to 32 weeks, sensitivity and specificity for preterm birth before 34 weeks were 78% and 66% respectively for 35 mm, 41% and 87% for 30 mm, 36% and 94% for 25 mm, and 30% and 94% for 20 mm [55].

Melamed et al. assessed the change in cervical length over a series of time-points. In all, 441 asymptomatic women with twin pregnancies underwent transvaginal ultrasound assessment of cervical length at four time-points between 18 and 32 weeks gestation. A short cervix (<10^{th} percentile) was associated with preterm birth at <32 weeks gestation in each of the four time-points assessed. A stepwise algorithm integrating serial cervical length measurements from all four time-points resulted in a significant increase in the area under the receiver operating characteristic (ROC) curve (0.917 vs 0.613; $P < 0.001$) [56]. This group also found that the pattern of cervical shortening correlated with prediction of preterm birth: early shortening was associated with the highest prediction of preterm birth [57].

Findings of progressive cervical shortening correlating with preterm birth were also supported by Moroz et al. They assessed 527 women with twin pregnancies who had undergone serial cervical measurements between 18 and 22 weeks gestation, finding that the rate of change in cervical length was associated with preterm birth <35 weeks gestation (–0.21 cm/week (SD: 0.27) vs –0.1 cm/week (SD 2.4) for women who delivered >35 weeks. The change in cervical length was similarly predictive of spontaneous preterm birth irrespective of whether the initial length was short as defined by the ROC analysis in this cohort [58].

The timing of ultrasound scans has been shown to be relevant. An individual patient-level meta-analysis assessing the effect of gestational age and cervical length measurements using transvaginal ultrasound in the prediction of preterm birth in twin pregnancies found that the optimal prediction of birth ≤28 weeks was enabled by screening at ≤18 weeks ($P < 0.001$), whereas the best prediction of birth between 28 and 36 weeks was enabled by screening at ≥24 weeks ($P < 0.001$) [59]. Negative predictive value of 100% for birth at ≤28 weeks was achieved at 65 mm at ≤18 weeks, and 43 mm at 22–24 weeks, respectively.

5.1.2. Additional ultrasound parameters

Other ultrasound parameters have been assessed as predictors for asymptomatic women with multiple pregnancies. Cervical funnelling has been found to be associated with an increased risk of preterm delivery <35 weeks detected prior to 24 weeks gestation [60], and the presence of amniotic fluid sludge in the presence of a short cervix has also been found to correlate with extreme prematurity [61].

5.2. Biomarkers

5.2.1. Fetal fibronectin

A meta-analysis conducted in 2010 of 11 studies evaluating fFN suggested only minimal predictive value for its use in asymptomatic twin pregnancies: the pooled sensitivities, specificities and positive and negative likelihood ratios for predicting preterm birth before 32, 34 and 37 weeks ranged from 33% to 45%, 80% to 94%, 2.0 to 5.5 and 0.68 to 0.76 [54]. These findings were confirmed by a 2018 meta-analysis which incorporated five studies assessing asymptomatic women with multiple pregnancies ($n = 1427$). The accuracy of fFN was found to be inconclusive: none of the studies used a reference standard defined as birth before 37 weeks; most defined preterm birth in the context of a delivery before 32 weeks and two studies evaluated triplet pregnancies – therefore the data were heterogeneous [62].

It has been shown that the combination of cervical length and fFN may be useful in predicting women at high risk of preterm birth. One study found that in asymptomatic women with a short cervix ≤25 mm at 22–28 weeks, and positive fFN, there was a strong association

with preterm delivery <32 weeks gestation (46.2 versus 12.6%; aOR: 3.54; 95% CI: 1.26–9.92) and the mean gestational age at delivery was significantly earlier (31.1 versus 35.2; $P < 0.001$) [63]. Fox et al. also found that a combination of positive fibronectin result 22–32 weeks gestation and a cervical length <20 mm in twin pregnancies had a higher positive predictive value of preterm delivery at all gestational ages (<37, <34, <32, <30 and <28 weeks) than either positive test alone [64]. This finding also applied to a series of 39 women with triplet pregnancies [65].

Spiegelman et al. assessed the independent association of cervical length, fetal fibronectin amniotic fluid sludge, and cervical funnelling with spontaneous preterm birth in twin pregnancies [66]. They retrospectively assessed ultrasound images from 22 to 26 weeks gestation for the presence of a short cervix (defined as <25 mm), cervical funnelling, and fibronectin from 635 twin pregnancies, finding the presence of sludge, a positive fetal fibronectin, and short cervix correlated with birth <35 weeks gestation.

6. Multiple pregnancies: symptomatic women in threatened preterm labour

6.1. Ultrasound parameters

The use of cervical length measurement as a predictive tool in symptomatic twin pregnancies for preterm birth has been shown to be of limited value. The meta-analysis by Conde-Agudelo assessed five studies in symptomatic twin pregnancies ($n = 310$), finding that the predictive accuracy of cervical length was low [53].

The presence of cervical funnelling was also found to have little predictive value in symptomatic women with twin pregnancies [67].

6.2. Biomarkers

Fetal fibronectin (fFN) has also been shown to be beneficial in predicting preterm delivery in symptomatic women with multiple pregnancies. A meta-analysis of four studies of such women showed it to have a pooled sensitivity, specificity and positive and negative likelihood ratios of 85%, 78% 3.9 and 0.2, respectively [54]. In a study of 40 women with multiple pregnancies, with symptoms of preterm labour presenting between 24 and 33^{+6} weeks gestation, patients were assessed with both fFN testing and cervical length assessment. The cervical length was not found to be predictive of PTB but fFN had a sensitivity of 66.7%, specificity of 97.2%, a positive predictive value of 66.7% and negative predictive value of 97.2% of delivery within seven days. Combined cervical length and fFN did not improve prediction [68].

Conclusions

Accurate prediction of the risk of preterm birth among asymptomatic high-risk women and those who are symptomatic with threatened preterm labour will allow us to target

interventions and give treatment to those most likely to benefit. Unfortunately, there is no "one-size fits all" test for predicting preterm birth but a combination of tests, particularly biomarkers and cervical length, is likely to improve prediction and clinical utility (summarised in Table 1). The population tested, i.e. symptomatic or asymptomatic, will also determine which test performs best. As our research community focuses more on understanding the different aetiologies and mechanisms of preterm birth, our knowledge of how to best predict preterm birth in these different scenarios will also evolve.

Practice points

- Many predictive tests for preterm birth are available clinically.
- Efficacy of these tests are likely to depend on the purpose of the prediction, i.e. asymptomatic high-risk women or symptomatic women in threatened preterm labour.
- The best predictive tests in singleton and multiple pregnancies are likely to differ.
- A combination of cervical length and biomarkers is likely to improve predictive efficacy of preterm birth.

Research directions

- Studies comparing a combination of predictive tests.
- Larger studies for assessing predictive test efficacy.
- Development of novel markers that can direct prophylactic intervention.

Conflict of interest statement

None declared.

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References

[1] Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. Br Med J 2012;345:217–24.

[2] Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1:S2.

[3] Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.

[4] GBD 2015 DALYs and HALE Collaborators, Kassenbaum NJ, Arora M, Barber RM, et

al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1603–58.

[5] Moutquin JM. Classification and heterogeneity of preterm birth. Br J Obstet Gynaecol 2003;110:30–3.

[6] Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. Br J Obstet Gynaecol 2006;113:17–42.

[7] Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol 2014;210:131.e1–131.e8.

[8] Medley N, Poljak B, Mammarella S, Alfirevic Z. Clinical guidelines for prevention and management of preterm birth: a systematic review. Br J Obstet Gynaecol 2018;125:1361–9.

[9] Owen J, Yost N, Berghella V, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA 2001;286:1340–8.

[10] Smith GCS, Celik E, To M, Khouri O, Nicolaides KH. Cervical length at mid-pregnancy and the risk of primary cesarean delivery. N Engl J Med 2008;358:1346–53.

[11] Goldenberg RL, Iams JD, Mercer BM, et al., National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. What we have learned about the predictors of preterm birth. Semin Perinatol 2003;27:185–93.

[12] Salomon LJ, Diaz-Garcia C, Bernard JP, Ville Y. Reference range for cervical length throughout pregnancy: non-parametric LMS-based model applied to a large sample. Ultrasound Obstet Gynecol 2009;33:459–64.

[13] Crane JMG, Hutchens D. Transvaginal sonographic measurement of cervical length to predict preterm birth in asymptomatic women at increased risk: a systematic review. Ultrasound Obstet Gynecol 2008;31:579–87.

[14] Iams JD, Grobman WA, Lozitska A, et al. Adherence to criteria for transvaginal ultrasound imaging and measurement of cervical length. Am J Obstet Gynecol 2013;209:365.e1–5.

[15] Souka AP, Papastefanou I, Michalitsi V, Salambasis K, Chrelias C, Salamalekis G, Kassanos D. Cervical length changes from the first to second trimester of pregnancy, and prediction of preterm birth by first-trimester sonographic cervical measurement. J Ultrasound Med 2011;30:997–1002.

[16] Moroz LA, Simhan HN. Rate of sonographic cervical shortening and the risk of spontaneous preterm birth. Am J Obstet Gynecol 2012;206:234.e1–5.

[17] Wulff CB, Rode L, Rosthøj S, Hoseth E, Petersen OB, Tabor A. Transvaginal sonographic cervical length in first and second trimesters in a low-risk population: a prospective study. Ultrasound Obstet Gynecol 2018;51:604–13.

[18] Einerson BD, Grobman WA, Miller ES. Cost-effectiveness of risk-based screening for cervical length to prevent preterm birth. Am J Obstet Gynecol 2016;215:100.e1–7.

[19] Rozenberg P. Universal cervical length screening for singleton pregnancies with no history of preterm delivery, or the inverse of the Pareto principle. Br J Obstet Gynaecol 2017;124:1038–45.

[20] Esplin MS, Elovitz MA, Iams JD, et al. Predictive accuracy of serial transvaginal cervical lengths and quantitative vaginal fetal fibronectin levels for spontaneous preterm birth among nulliparous women. JAMA 2017;317:1047.

[21] Kuhrt K, Smout E, Hezelgrave N, Seed PT, Carter J, Shennan AH. Development and validation of a tool incorporating cervical length and quantitative fetal fibronectin to predict spontaneous preterm birth in asymptomatic high-risk women. Ultrasound Obstet Gynecol 2016;47:104–9.

[22] Adanir I, Ozyuncu O, Gokmen Karasu AF, Onderoglu LS. Amniotic fluid “sludge”; prevalence and clinical significance of it in asymptomatic patients at high risk for spontaneous preterm delivery. J Matern Neonatal Med 2018;31:135–40.

[23] Hatanaka AR, Mattar R, Kawanami TEN, et al. Amniotic fluid “sludge” is an independent risk factor for preterm delivery. J Matern Neonatal Med 2016;29:120–5.

[24] Kusanovic JP, Espinoza J, Romero R, et al. Clinical significance of the presence of amniotic fluid “sludge” in asymptomatic patients at high risk for spontaneous preterm delivery. Ultrasound Obstet Gynecol 2007;30:706–14.

[25] Baños N, Julià C, Lorente N, Ferrero S, Cobo T, Gratacos E, Palacio M. Mid-trimester cervical consistency index and cervical length to predict spontaneous preterm birth in a high-risk population. Am J Perinatol Reports 2018;8:e43–50.

[26] Goldenberg RL, Iams JD, Das A, et al. The Preterm Prediction Study: sequential cervical length and fetal fibronectin testing for the prediction of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Am J Obstet Gynecol 2000;182:636–43.

[27] Abbott DS, Hezelgrave NL, Seed PT, et al. Quantitative fetal fibronectin to predict preterm birth in asymptomatic women at high risk. Obstet Gynecol 2015,125:1168–76.

[28] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.

[29] Wei S, Fraser W, Luo Z. Inflammatory cytokines and spontaneous preterm birth in

asymptomatic women: a systematic review. Obstet Gynecol 2010;116:393–401.

[30] Amabebe E, Chapman DR, Stern VL, Stafford G, Anumba DOC. Mid-gestational changes in cervicovaginal fluid cytokine levels in asymptomatic pregnant women are predictive markers of inflammation-associated spontaneous preterm birth. J Reprod Immunol 2018;126:1–10.

[31] Kindinger LM, Bennett PR, Lee YS, et al. The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk. Microbiome 2017;5:6.

[32] Elovitz MA, Brown AG, Anton L, Gilstrop M, Heiser L, Bastek J. Distinct cervical microRNA profiles are present in women destined to have a preterm birth. Am J Obstet Gynecol 2014,210:221.e1–11.

[33] Ghartey J, Bastek JA, Brown AG, Anglim L, Elovitz MA. Women with preterm birth have a distinct cervicovaginal metabolome. Am J Obstet Gynecol 2015,212:776.e1–12.

[34] National Institute for Health and Care Excellence. Preterm labour and birth. London: NICE; 2015.

[35] Berghella V, Palacio M, Ness A, Alfirevic Z, Nicolaides KH, Saccone G. Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol 2017;49:322–9.

[36] DeFranco EA, Lewis DF, Odibo AO. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. Am J Obstet Gynecol 2013;208:233.e1–6.

[37] Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. Am J Obstet Gynecol 2013,208:122.e1–6.

[38] Watson HA, Carter J, Seed PT, Tribe RM, Shennan AH. The QUiPP App: a safe alternative to a treat-all strategy for threatened preterm labor. Ultrasound Obstet Gynecol 2017;50:342–6.

[39] Bruijn M, Vis J, Wilms F, et al. Quantitative fetal fibronectin testing in combination with cervical length measurement in the prediction of spontaneous preterm delivery in symptomatic women. Br J Obstet Gynaecol 2016;123:1965–71.

[40] Levine LD, Downes KL, Romero JA, Pappas H, Elovitz MA. Quantitative fetal fibronectin and cervical length in symptomatic women: results from a prospective blinded cohort study. J Matern Neonatal Med 2018 May 15:1–9 [Epub ahead of print].

[41] van Baaren G-J, Vis JY, Wilms FF, et al. Cost-effectiveness of diagnostic testing strategies including cervical-length measurement and fibronectin testing in women with symptoms of preterm labor. Ultrasound Obstet Gynecol 2018;51:596–603.

[42] Akercan F, Kazandi M, Sendag F, Cirpan T, Mgoyi L, Terek MC, Sagol S. Value of cervical phosphorylated insulinlike growth factor binding protein-1 in the prediction of preterm labor. J Reprod Med 2004;49:368–72.

[43] Conde-Agudelo A, Romero R. Cervical phosphorylated insulin-like growth factor binding protein-1 test for the prediction of preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol 2016;214:57–73.

[44] Kumari A, Saini V, Jain PK, Gupta M. Prediction of delivery in women with threatening preterm labour using phosphorylated insulin-like growth factor binding protein-1 and cervical length using transvaginal ultrasound. J Clin Diagn Res 2017;11:QC01–QC04.

[45] Fuchs F, Houllier M, Leparco S, Guyot A, Senat M-V, Fernandez H. Performance of cervical phIGFBP-1 test alone or combined with short cervical length to predict spontaneous preterm birth in symptomatic women. Sci Rep 2017;7:10856.

[46] Wing DA, Haeri S, Silber AC, et al. Placental alpha microglobulin-1 compared with fetal fibronectin to predict preterm delivery in symptomatic women. Obstet Gynecol 2017;130:1183–91.

[47] Melchor JC, Navas H, Marcos M, et al. Predictive performance of PAMG-1 vs fFN test for risk of spontaneous preterm birth in symptomatic women attending an emergency obstetric unit: retrospective cohort study. Ultrasound Obstet Gynecol 2018;51:644–9.

[48] Ravi M, Beljorie M, El Masry K. Evaluation of the quantitative fetal fibronectin test and PAMG-1 test for the prediction of spontaneous preterm birth in patients with signs and symptoms suggestive of preterm labor. J Matern Neonatal Med 2018 May 28:1–6 [Epub ahead of print].

[49] Amabebe E, Reynolds S, Stern V, Stafford G, Paley M, Anumba DOC. Cervicovaginal fluid acetate: a metabolite marker of preterm birth in symptomatic pregnant women. Front Med 2016;3:48.

[50] Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. N Engl J Med 1995;333:1737–42.

[51] Stock S, Norman J. Preterm and term labour in multiple pregnancies. Semin Fetal Neonatal Med 2010;15:336–41.

[52] Facco F, Nash K, Grobman W. Are women who have had a preterm singleton delivery at increased risk of preterm birth in a subsequent twin pregnancy? Am J Perinatol

2008,25:657–9.

[53] Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203:128.e1–12.

[54] Conde-Agudelo A, Romero R. Cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in multiple pregnancies: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2010;23:1365–76.

[55] Lim AC, Hegeman MA, Huis In 'T Veld MA, Opmeer BC, Bruinse HW, Mol BWJ. Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol 2011;38:10–17.

[56] Melamed N, Pittini A, Hiersch L, Yogev Y, Korzeniewski SJ, Romero R, Barrett J. Do serial measurements of cervical length improve the prediction of preterm birth in asymptomatic women with twin gestations? Am J Obstet Gynecol 2016;215:616.e1–14.

[57] Melamed N, Pittini A, Hiersch L, Yogev Y, Korzeniewski SS, Romero R, Barrett J. Serial cervical length determination in twin pregnancies reveals 4 distinct patterns with prognostic significance for preterm birth. Am J Obstet Gynecol 2016;215:476.e1–11.

[58] Moroz LA, Brock CO, Govindappagari S, Johnson DL, Leopold BH, Gyamfi-Bannerman C. Association between change in cervical length and spontaneous preterm birth in twin pregnancies. Am J Obstet Gynecol 2017;216:159.e1–7.

[59] Kindinger LM, Poon LC, Cacciatore S, et al. The effect of gestational age and cervical length measurements in the prediction of spontaneous preterm birth in twin pregnancies: an individual patient level meta-analysis. Br J Obstet Gynaecol 2016;123:877–84.

[60] Asnafi N, Basirat Z, Hajian-Tilaki K, Dadvar S. Assessment of cervical length by transvaginal ultrasonography to predict preterm delivery in twin pregnancy. J Matern Neonatal Med 2013;26:1435–8.

[61] Boyer A, Cameron L, Munoz-Maldonado Y, et al. Clinical significance of amniotic fluid sludge in twin pregnancies with a short cervical length. Am J Obstet Gynecol 2014;211:506.e1–9.

[62] Dos Santos F, Daru J, Rogozińska E, Cooper NAM. Accuracy of fetal fibronectin for assessing preterm birth risk in asymptomatic pregnant women: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2018;97:657–67.

[63] Matthews KC, Gupta S, Lam-Rachlin J, Saltzman DH, Rebarber A, Fox NS. The association between fetal fibronectin and spontaneous preterm birth in twin pregnancies with a shortened cervical length. J Matern Neonatal Med 2018;31:2564–8.

[64] Fox NS, Saltzman DH, Klauser CK, Peress D, Gutierrez CV, Rebarber A. Prediction of spontaneous preterm birth in asymptomatic twin pregnancies with the use of combined fetal fibronectin and cervical length. Am J Obstet Gynecol 2009;201:313.e1–5.

[65] Fox NS, Rebarber A, Roman AS, Klauser CK, Peress D, Saltzman DH. Combined fetal fibronectin and cervical length and spontaneous preterm birth in asymptomatic triplet pregnancies. J Matern Fetal Neonatal Med 2012;25:2308–11.

[66] Spiegelman J, Booker W, Gupta S, et al. The independent association of a short cervix, positive fetal fibronectin, amniotic fluid sludge, and cervical funneling with spontaneous preterm birth in twin pregnancies. Am J Perinatol 2016;33:1159–64.

[67] Vendittelli F, Mamelle N, Munoz F, Janky E. Transvaginal ultrasonography of the uterine cervix in hospitalized women with preterm labor. Int J Gynaecol Obstet 2001;72:117–25.

[68] Fuchs F, Lefevre C, Senat M-V, Fernandez H. Accuracy of fetal fibronectin for the prediction of preterm birth in symptomatic twin pregnancies: a pilot study. Sci Rep 2018;8:2160.

Table 1. Summary of predictive preterm birth tests.

Test	Singleton pregnancy		Multiple pregnancy	
	Asymptomatic high risk	Symptomatic threatened PTL	Asymptomatic high risk	Symptomatic threatened PTL
Cervical length	+	+	+	
fFN	+	+	+	+
Cervical length + fFN	++	++	+	
PIGFBP-1		+		
PAMG-1		+		

PTL, preterm labour; fFN, fetal fibronectin; PIGFBP-1, phosphorylated insulin-like growth factor binding protein-1; PAMG-1, placental alpha-macroglobulin-1.